

**Marked-Up Copy of Replacement Specification Paragraphs,  
as Amended in the Preliminary Amendment Filed Herewith**

*Paragraph [0047] has been amended as follows.*

[0047] Figure 1, comprising Figures 1A, 1B, 1C, 1D, 1E, and 1F, depict binding of hMSH2:hMSH6 heterodimer to mismatched and non-mismatched duplex DNA. Figure 1A is an image of the results of a gel mobility shift assay performed using the G/T-mismatched 81-base pair duplex DNA substrate described herein. The concentrations of heterodimer used in the assay ~~are indicated along the top of the image~~ were, in nanomolar, 0 in A, 6 in B, 19 in C, 32 in D, 64 in E, 97 in F, 129 in G, 161 in H, 193 in I, 257 in J, and 322 in K. The position of the S-shifted electrophoretic band is indicated by "S". Figure 1E is a graph which depicts the relationship between the concentration of heterodimer and the amount of product corresponding to the S-shifted electrophoretic band in Figure 1A, as assessed using a phosphoimaging device. Figure 1B is an image of the results of a gel mobility shift assay performed using the homologous 81-base pair duplex DNA substrate described herein. The concentrations of heterodimer used in the assay ~~are indicated along the top of the image~~ were, in nanomolar, 0 in A, 6 in B, 19 in C, 32 in D, 64 in E, 129 in F, 225 in G, 322 in H, 386 in I, and 482 in J. The position of the NS-shifted electrophoretic band is indicated by "NS". Figure 1F is a graph which depicts the relationship between the concentration of heterodimer and the amount of product corresponding to the NS-shifted electrophoretic band in Figure 1B, as assessed using a phosphoimaging device. Figure 1C is an image which depicts the results of a DNase footprint assay performed using the 81-base pair G/T-mismatched duplex DNA substrate described herein. The concentrations of 81-base pair ~~are indicated along the top of the image~~ were, in nanomolar, 0 in A, 13 in B, 32 in C, and 97 in D. The position of the G residue of the G/T-mismatched substrate is indicated by "G", and the approximate region of the substrate protected from DNase cleavage by the heterodimer is indicated by a vertical line. Figure 1D is an image which depicts the results of a DNase footprint assay performed using the homologous 81-base pair duplex DNA substrate described herein. The concentrations of heterodimer used in the assay ~~are indicated along the top of the image~~ were, in nanomolar, 0 in A, 161 in B, 322 in C, and 482 in

D. The position of the G/C base pair corresponding to the G/T-mismatched base pair of the mismatched substrate is indicated by "G".

*Paragraph [0048] has been amended as follows.*

[0048] Figure 2, comprising Figures 2A, 2B, 2C, and 2D, depicts the results of gel mobility shift assays used to assess the ability of various adenine nucleotides to dissociate MSH dimer from the mismatch site, corresponding to the S-shifted electrophoretic band, such that the MSH dimer, corresponding to the NS-shifted electrophoretic band, exhibited DNA-associated diffusion. Figure 2A is an image of an assay in which the product corresponding to the S-shifted electrophoretic band was incubated in the presence of ATP at the following concentration-listed along the top of the image, in micromolar, 0 in A and B, 0.5 in C, 1 in D, 2 in E, 3.9 in F, 7.8 in G, 15.6 in H, 31.3 in I, 62.5 in J, and 125 in K. Figure 2B is an image of an assay in which the product corresponding to the S-shifted electrophoretic band was incubated in the presence of adenosine-5'-O-3'-thiotriphosphate (ATP- $\gamma$ -S) at the following concentration-listed along the top of the image, in micromolar, 0 in A and B, 0.5 in C, 1 in D, 2 in E, 3.9 in F, 7.8 in G, 15.6 in H, 31.3 in I, 62.5 in J, and 125 in K. Figure 2C is an image of an assay in which the product corresponding to the S-shifted electrophoretic band was incubated in the presence of ADP at the following concentration-listed along the top of the image, in micromolar, 0 in A and B, 25 in C, and 100 in D. In lane A of each of Figures 2A, 2B, and 2C, "-" indicates that no heterodimer was included in the assay mixture. Figure 2D is a graph which depicts quantitated results obtained using the results depicted in Figures 2A, 2B, and 2C, as assessed using a phosphoimaging device.

*Paragraph [0052] has been amended as follows.*

[0052] Figure 6, comprising Figures 6A, 6B, 6C, and 6D, depicts the results of experiments performed to assess the effects of ATP, homologous DNA, or both, on the dissociation of the hMSH2:hMSH6 heterodimer from DNA. Figure 6A is an image of the results obtained from gel mobility shift assays in which heterodimer-bound mismatched DNA was incubated with ATP for the following time indicated in the image, in minutes, 0 in A and B, 0.5 in C, 1 in D, 2 in E, 3 in

F, 4 in G, 5 in H, 7.5 in I, and 10 in J. Figure 6B is an image of the results obtained from gel mobility shift assays in which heterodimer-bound mismatched DNA was incubated with ATP and a 400-fold excess of homologous DNA for the following time indicated in the image, in minutes, 0 in A and B, 0.5 in C, 1 in D, 2 in E, 3 in F, 4 in G, 5 in H, 7.5 in I, and 10 in J. Figure 6C is an image of the results obtained from gel mobility shift assays in which heterodimer-bound mismatched DNA was incubated with a 400-fold excess of homologous DNA for the following time indicated in the image, in minutes, 0 in C, 5 in D, and 10 in E. Figure 6D is an image of the results obtained from gel mobility shift assays in which the heterodimer was incubated with homoduplex DNA probe for fifteen minutes at 37°C (Lane A B), the assay mixture was cooled to 4°C, and a 1,100-fold excess of unlabeled competitor homoduplex DNA was added (Lane B C). In each of Figure 6A, 6B, 6C, and 6D, """ indicates the assay mixtures which corresponding to lane A did not comprise the heterodimer.

*Paragraph [0054] has been amended as follows.*

[0054] Figure 8, comprising Figures 8A, 8B, 8C, and 8D, lists the nucleotide sequence of single nucleotide chains of some of the 39- and 81-base pair DNA substrates described herein (SEQ ID NOS: 2, 3, 5, and 6). Figure 8A lists SEQ ID NO: 2. Figure 8B lists SEQ ID NO: 3. Figure 8C lists SEQ ID NO: 5. Figure 8D lists SEQ ID NO: 6.

*Paragraph [0064] has been amended as follows.*

[0064] Figure 18 is a diagram which illustrates a model of hMSH2 consensus interaction with hMSH3 or hMSH6. The interaction regions of hMSH2, hMSH3, and hMSH6 are indicated in gray and are connected with lines that illustrate the specificity of each region to its corresponding interaction partner region. The nucleotide binding regions of hMSH2, hMSH3, and hMSH6 are indicated as black boxes. The location of HNPCC-associated mutations tested in these studies are illustrated as black diamonds.

*Paragraph [0065] has been amended as follows.*

[0065] Figure 19, comprising Figures 19A, ~~19B, and 19C~~ through 19G, lists the nucleotide sequence of cDNA encoding hMSH5 (SEQ ID NO: 30) and the putative amino acid sequence of hMSH5 (SEQ ID NO: 29).

*Paragraph [0101] has been amended as follows.*

[0101] The invention relates to a method of modifying a mismatched duplex DNA. The method comprises contacting a MutS homolog (MSH) dimer and the mismatched duplex DNA in the presence of a binding solution. The binding solution comprises either ADP and ATP, and the concentration of ATP in the binding solution is less than 5 micromolar, less than about 3 micromolar, 1 micromolar or less, preferably less than about 0.3 micromolar, and more preferably wherein the binding solution is substantially free of ATP. Alternately, ADP is used in the absence of ATP, or at least in excess with respect to ATP (i.e. ADP at a 2-fold, 10-fold, or 100-fold or greater excess relative to ATP). The MSH dimer thereby binds ADP. When the ADP-bound MSH dimer is contacted with the mismatched duplex DNA, the dimer associates with the mismatched region of the DNA, thus forming a modified mismatched duplex DNA.

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**Marked-Up Copy of Claim 48**

48. (Amended) A cell line which is nullizygous for both Msh2 and p53, does not express Msh2 or p53, and exhibits a phenotype selected from the group consisting of a predisposition for carcinogenesis and a predisposition for apoptosis, wherein said cell line is made by culturing a cell obtained from the nonhuman mammal of claim-~~56~~ 44.

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